REMARKS

Reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.114, are respectfully requested.

Claims 1, 13, and 14 are under consideration in this application. Claims 15, and 17-30 have been withdrawn from consideration.

Response to Rejections Under 35 U.S.C. §103

Claims 1, 13, and 14 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Goodman et al. (PCT International Publication No. WO/27960) in view of Fleischer (1999, Abstract Only) or Fleischer (1999); and Miller et al. (1980 Abstract Only) and further over Canadian Patent 2161737 ("MacKay et al."). The rejection is respectfully traversed.

The Office has asserted that Goodman et al. teach a viscous hydrogel composition containing nitroimidazole (e.g. tinidazole) for treating inflamed skin diseases such as rosacea and eczema, and Example 1 uses about 0.75wt% of tinidazole. OFFICE ACTION DATED MAY 14, 2008. However, Goodman only demonstrated that a nitroimidazole gel composition comprising metronidazole or tinidazole can be used in the treatment of particular forms of eczema and rosacea. Goodman presented no working examples wherein atopic dermatitis is treated, nor suggested use of metronizadole in a concentration as high as 1.5 to 5wt%.

Neither of Fleischer and Miller suggests that a preparation containing 1.5 to 5% by weight of the nitroimidazole derivative can treat atopic dermatitis. The cited secondary references do not cure the deficiencies of Goodman et al., because the combination of those

references would not have overcome the accepted wisdom in the art that different forms dermatitis require different treatments and that atopic dermatitis is particularly difficult to treat.

The Fleischer 1999 abstract of a review of treatments of atopic dermatitis refers to the disadvantages of topical corticosteroids, which had been used because of their broad immunomodulatory effects, and relative advantages of tacrolimus in treating atopic dermatitis. However, neither corticosteroids nor tacrolimus are directly related to the compounds recited in the present claims. The Office has alleged that the Fleischer 1999 abstract teaches that immunosuppressants generally are effectively used in the treatment of atopic dermatitis. OFFICE ACTION DATED JULY 16, 2003, at 5. However, broad acting immune suppressants were known to cause undesired side effects as Fleischer indicated in the abstract. Thus, the Fleischer 1999 abstract can not be interpreted as suggesting the use of any compounds other than the particular compounds that had previously been found to be useful in treating atopic dermatitis.

The Miller 1980 abstract refers to a scientific publication directed to a study of five imdiazole compounds in an *in vitro* system to test whether the compounds affected the response of human lymphocytes to compounds or cells that were known to promote blast transformation, a step in process of immune reaction stimulation. The Office has alleged that the Miller 1980 abstract teaches that tinidazole is an effective immunosuppressant *in vivo*. However, that conclusion is erroneous. The Miller 1980 abstract does not show that any imidazole compounds can be used as immunosupressants *in vivo*, because the study described in the abstract is an *in vitro* study using cell cultures. Miller merely suggested that such studies could be used for screening compounds that might be investigated as immunosupressants *in vivo*. Miller does not suggest that the reported experiments are conclusive that any compound can be used in any

treatment. Indeed some compounds, including those recited in claim 1 produced results suggesting immunostimulatory activity.

More particularly, tinidazole and metronidazole were actually reported by Miller to enhance the immune cells response to stimulation by plant mitogens. Thus, the results reported by Miller would suggest, if anything, that tinidazole and metronidazole could have immunostimulatory effects *in vivo*. Consequently, if the alleged implications of the Fleischer 1999 abstract under the theory propounded by the Office would have had any influence on a person of ordinary skill in the art, then the Miller study would have suggested that tinidazole and metronidazole were actually unsuitable. That is, the results reported by Miller are actually contrary to the alleged basis for the rejection.

Nevertheless, the Office has contended that it would be obvious to treat atopic dermatitis using the treatment of Goodman et al. OFFICE ACTION DATED MAY 14, 2008, at 3. The Office cited Canadian Patent 2161737 ("MacKay et al.") alleging that MacKay et al. teaches the use of the topical formulation of metronidazole at the concentration of 5% topical suspension for the treatment of inflammatory skin conditions.

Applicants pointed out that MacKay et al. is directed to a gel for the treatment of rosacea and acne, not atopic dermatitis. See, MacKay et al. at Abstract. MacKay et al. teaches a 1.0% metronidazole gel with sunscreen for the treatment of rosacea and acne. (see page 9, line 23, and page 12, line 16) The single reference in the background of MacKay et al. to the prior existence of a 5% suspension does not constitute any suggestion to actually use that suspension in the treatment of even rosacea let alone atopic dermatitis. In the Office Action dated October 2, 2009, the Office has indicated that MacKay et al. was simply cited as evidence that

metornidazole has been previously used at the concentrations recited in the claims. The Office contends that, therefore, it would have been obvious to use such concentrations for the treatment of *any* inflammatory skin condition.

Thus, the current position of the Office rests upon the assumption that all inflammatory skin conditions are similar and may be treated similarly. The Office's current position actually contradicts its own actions and previous findings of fact in this application. The Office previously correctly determined that treatments of different skin diseases are patentably distinct, particularly with respect to those that were recited in original claims 16-30 of the present application, "because each skin condition [is] caused by different etiology and the treatment could be different, as evidence by numerous documents." OFFICE ACTION MAILED MARCH 25, 2003, at 2. Applicants elected without traverse the species of atopic dermatitis. REPLY FILED APRIL 24, 2003, at 2. The Examiner made the restriction requirement that was based upon this determination final. OFFICE ACTION MAILED JULY 16, 2003, at 2. Therefore, in accordance with the Office's own factual determination, a treatment of any of the different forms of dermatitis does not suggest a treatment of another form of dermatitis, each type of dermatitis having different causes and symtoms.

The evidence submitted herewith together with evidence already of record demonstrates that persons of skill in the art would understand that the causes, diagnosis and treatment of atopic dermatitis, which the claimed methods are directed to, are clearly distinct from the diagnosis, causes, and treatments of rosacea, which is addressed in the cited art.

Exhibit A (Leung et al., Annals of Allergy, Asthma, and Immunology, 93:S1-S21, 2004) and Exhibit B (Ellis et al., British Journal of Dermatology, 148(Suppl. 63):3-10, 2003) present

two examples of scholarly writings in the field, which demonstrate the unique etiologies and treatment difficulties associated with atopic dermatitis. By contrast Exhibit C (Cohen et al., JABFP, 15:214-17 2002) and Exhibit D (Culp et al., P&T, 34:38-34, 2009) present scholarly writings in the field that demonstrate that rosacea is a separate and distinct disorder from atopic dermatitis with distinct etiologies and treatments. For example, in Exhibit D, Table 2 presents a list of differential diagnoses which lists atopic dermatitis as a disease that must be excluded for a proper diagnosis of rosacea.

Furthermore, Exhibits A and B review the state of the understanding of the art of treatments of atopic dermatitis at a time following the present invention. Notably absent from these reviews of the state of the art are any suggestion of the presently claimed methods. This is further objective evidence that the presently claimed methods were not obvious at the time the invention was made. The present inventors were the first to succeed in the treatment of atopic dermatitis by use of a preparation containing 1.5 to 5% by weight of nitroimidazole derivative. The surprising effectiveness is shown in Test Examples 1 to 8 in the present specification. Because of the recognized difficulty of treating atopic dermatitis and the general view in the art at the time that no more that about 0.75 - 1 % of a nitroimidazole derivative should be used, the results disclosed by the present inventors were not expected in the art. None of the cited references separately or together would have predicted the results obtained by the inventors. Therefore, the present invention could not have been obvious from the cited references.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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